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ESTIMATION OF PARAMETERS IN MULTIVARIATE EXPERIMENTAL DESIGN AND A HYPOTHETICAL APPLICATION TO ESTIMATING FRACTIONAL DOSE RECOVERY EFFECTS

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DESIGN AND A HYPOTHETICAL APPLICATION TO ESTIMATING

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ABSTRACT

A statistical technique is explained, derived and illustrated. It is believed that a study of the values of the terms of the assumed mathematical model (or the graphs therefrom) would be of great informational help to the scientist in interpreting his results. Analysis of variance, components of variance analysis, and the estimation technique described herein applied to a properly designed experiment will go far toward extracting all the relevant information from a sample.

Estimation formulas for the terms of the assumed mathematical model are derived for two of the most used statistical experimental designs, the factorial and the orthogonal squares. The method is illustrated on a three-variable, hypothetical dose recovery experiment.

It is pointed out that the method gives one a handle on measuring quantitatively the separate and joint contributions to the observed effect, of variables otherwise hopelessly correlated and overlapping.

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I. INTRODUCTION

Considerations like those discussed herein tend to reduce the material requirements of research projects as the methods and implications of such planning and analyses become more familiar. It becomes a case of more prior thinking and planning for the experiment, and less data. One hardly needs to point out that the number of experimental animals to be housed and cared for and personnel and equipment to process them for data acquisition are of prime consideration in setting space requirements in the Armed Forces Radiobiology Research Institute (AFRRI) laboratories. Faced with known space limitations, it is imperative that we do the best we can to maximize the amount and definitiveness of experimental results.

It is quite likely true that the most definitive experiments to test for rejection of alternative branch routes up the tree of hypotheses, making up the bases of a scientific field, are far more logical in character than mathematical. Nevertheless, much AFRRI research will involve the next stage, which is to measure and quantify properties or effects already known or suspected to exist. Considering the interrelationships of variables, this is no easy task.

A systematic approach to the latter stage is to set up a general mathematical model considered appropriate to the situation, test its components for existence and consequent specialization of the model, and finally, estimate the numerical values of parameters of the model. This procedure represents efficient use of information because the models represent a common means of determining facts from experiment and for suggesting new angles requiring investigation. This paper introduces the scientist to a small region of mathematical statistics germane to the latter procedure.

II. THE PROBLEM

In many statistically designed multivariate experiments, analysis of variance gives the appropriate significance tests of the effects of the variables and interactions. The experimenter may then wish to display his findings tabularly and/or graphically. It would seem that this display is not necessarily just to show the observed results in another manner, but that the display should imply the fundamental, underlying basic relationships of which his test data are merely a sample. The aforementioned analysis of variance gives the experimenter reasonable assumptions as to the specialized form of the mathematical model describing these basic relationships.

This methodological paper shows how one can find the various terms of the mathematical model. They are least squares estimates. Then from these estimates the experimenter can show values or graphs having the properties assumed or learned from the analysis of variance, and which also fit his data best in the sense of least squares.

III. DISCUSSION

We restrict ourselves to 'fixed' rather than 'random' variables. Thus a dose variable may have four assigned values - they are not randomly selected. Also, for the moment consider a complete factorial design illustrated as follows.

Let variable A denote the dose rates for a set of experiments. For instance, one might let $a_1 = 10$ rad/min and $a_2 = 100$ rad/min. The limit for the high dose rate would be the pulse mode of operation of the reactor. Variable B denotes the dose delivered in one period of fractionization. $b_1 = 20$ rads, $b_2 = 30$ rads, $b_3 = 40$ rads.

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The number of fractionated doses is to be a constant k. A graphic presentation of the exposures for a_1b_1 and a_2b_2 is shown below.
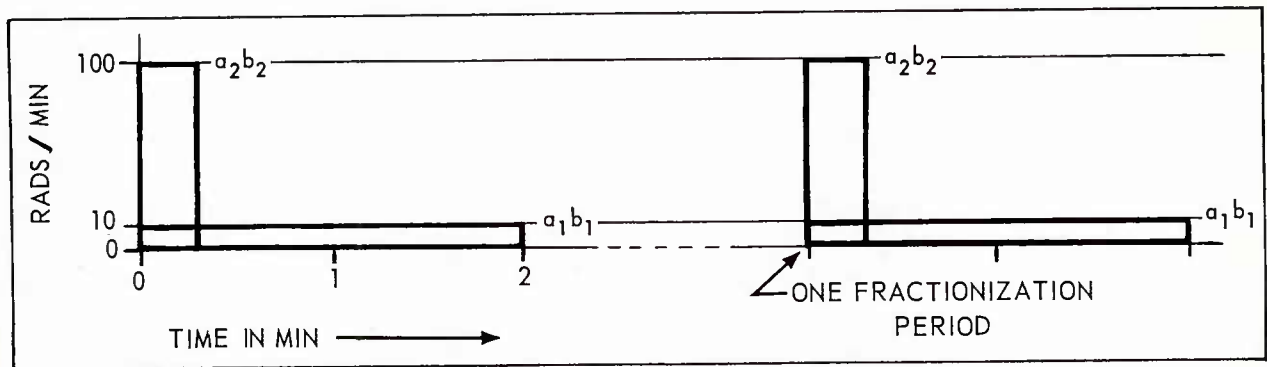
Figure 1. Graph of Exposures

The integrated dose at each condition a_i, b_j is simply b_jk.

All possible combinations of levels of the variables are used. At each of the 2 x 3 = 6 possible combinations of A, B, an $LD_{50/30}$ (= y) will be obtained. (If several values are found at each condition, the method of estimation described herein will be unchanged, but one considers only the averages at each condition.)

It has been found that a practical and satisfactory general representation of the combined several effects is of the form

(1) $$y_{ij} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + e_{ij} \; .$$

Let subscript i denote the level of variable A, thus i = 2 means 100 rad/min. Similarly, subscript j denotes the level of variable B, thus j = 1 means 20 rad dose per fractionization period. The terms in (1) represent independent contributions to the total y value at a_i, b_j. Each term on the right but the last one is an underlying average effect or value. μ, α_i, β_j, $(\alpha\beta)_{ij}$ are all fixed numbers, constants, which will be estimated from the data. One or more might be zero, depending on what one learned from

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the analysis of variance on the data in the first place, or could assume from past experience or knowledge. μ is a general average of y over the set of the independent variables A and B, common to all y values. α_i is a main effect (A) and can be so related to the μ that $\sum_i \alpha_i = 0$. Condition a_1 causes a contribution of α_1 to y_{13}, for example. Similarly $\sum_j \beta_j = 0$ and, for example, condition b_3 causes a contribution of β_3 to y_{13}.

$(\alpha\beta)_{ij}$ is called an interaction term, and when it exists causes a special contribution to y. Thus the value $(\alpha\beta)_{13}$ will be part of the sum of terms making up the total value of y_{13}. If there is no interaction then by definition all such terms are zero. It is further assumed that summing over any one interaction subscript while holding the other subscripts constant on any of their allowed values is zero. Thus $(\alpha\beta)_{13} + (\alpha\beta)_{23}$ = 0 in the example.

e_{ij} is a random normal variate with mean zero and variance generally labeled σ^2 and estimated from the experimental data by the analysis of variance.

At this time we will derive the estimates of the terms in (1) for the general two-variable factorial case. By specializing the number of levels of the variables to two and three, respectively, the results will be appropriate to the preceding example.

Obtaining the Least Squares Estimates of the Values in (1)

Let
$$m_{ij} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} \, .$$

Then (1) becomes

(2)
$$y_{ij} = m_{ij} + e_{ij} \, .$$

Let the number of levels of A and B be ℓ_1 and ℓ_2, respectively. Form the expression

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(3) $$A = \underset{\substack{i=1,\ldots,\ell_1 \\ j=1,\ldots,\ell_2}}{\Sigma} (y_{ij} - m_{ij})^2 = \underset{i,j}{\Sigma} e_{ij}^2 .$$

A true minimum exists at the necessary conditions obtained by setting the partials $\partial A/\partial \mu$, $\partial A/\partial \alpha_i$, $\partial A/\partial \beta_j$, $\partial A/\partial (\alpha\beta)_{ij}$ equal to zero. One of these will be written out in detail.

$$\partial A/\partial \alpha_i = -2 \underset{j}{\Sigma} (y_{ij} - \mu - \alpha_i - \beta_j - (\alpha\beta)_{ij}) = 0.$$

Then

$$\ell_2 \alpha_i = \underset{j}{\Sigma} y_{ij} - \ell_2 \mu - \underset{j}{\Sigma} \beta_j - \underset{j}{\Sigma} (\alpha\beta)_{ij} .$$

But by assumption, the last two terms are zero. Therefore,

$$\alpha_i = \frac{1}{\ell_2} \underset{j}{\Sigma} y_{ij} - \mu .$$

When one considers that he is solving a system of linear equations in terms of the y_{ij}, the results on μ, α_i, β_j, $(\alpha\beta)_{ij}$ are clearly estimates and are customarily labeled $\widehat{\mu}$, $\widehat{\alpha_i}$, etc. Thus

$$\widehat{\alpha_i} = \frac{1}{\ell_2} \underset{j}{\Sigma} y_{ij} - \widehat{\mu} .$$

In fact, the entire set of four answers will be found to be

(4)
$$\begin{cases} \widehat{\mu} = \dfrac{1}{\ell_1 \ell_2} \underset{i,j}{\Sigma} y_{ij} , \\[2mm] \widehat{\alpha_i} = \dfrac{1}{\ell_2} \underset{j}{\Sigma} y_{ij} - \widehat{\mu}, \ i = 1,\ldots,\ell_1 \\[2mm] \widehat{\beta_j} = \dfrac{1}{\ell_1} \underset{i}{\Sigma} y_{ij} - \widehat{\mu}, \ j = 1,\ldots,\ell_2 \\[2mm] \widehat{(\alpha\beta)}_{ij} = y_{ij} - \widehat{\mu} - \widehat{\alpha_i} - \widehat{\beta_j} . \end{cases}$$

These are the estimates of the effects due to the various levels of the individual variables and also when taken jointly. As an example, let us interpret the effect of

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b_2 on y_{12}. First we must recognize that each value y_{ij} has average value μ except for the addition to μ of the several other effects appearing in (1). The presence of level b_2 increases algebraically the average y_{12} from μ to $\mu + \beta_2$. However, when interaction exists, b_2 exerts an additional effect along with level a_1 to further increase (algebraically) the average y_{12} from $\mu + \beta_2$ to $\mu + \beta_2 + (\alpha\beta)_{12}$. A similar statement shows that level a_1 increases average y_{12} from $\mu + \beta_2 + (\alpha\beta)_{12}$ to $\mu + \beta_2 + (\alpha\beta)_{12} + \alpha_1$. Its effect jointly with b_2, namely, $(\alpha\beta)_{12}$, has already been added in. Since we have only estimates of each of these quantities, in practice the statements will read somewhat as follows: the presence of level b_2 is to increase (algebraically) the average y from estimated μ to estimated $(\mu + \beta_2)$, i.e., from $\widehat{\mu}$ to $\widehat{\mu} + \widehat{\beta_2}$.

If one turns back to the definition of m_{ij} he sees that it is the mean or underlying population average value at a_i, b_j without the variation due to σ of the individual readings. That is likewise an estimate that is quite useful. It can be found by replacing each component or term by its estimate as just found. So the estimate of

$$m_{ij} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} \quad \text{becomes}$$

(5)
$$\widehat{m_{ij}} = \widehat{\mu} + \widehat{\alpha_i} + \widehat{\beta_j} + \widehat{(\alpha\beta)}_{ij} \ .$$

All the above has been carried out in a generalization to n variables with $\ell_1, \ell_2, \ldots, \ell_n$ levels, respectively. The results, only, will now be stated.

The generalized $\widehat{m}_{i_1 \ldots i_n}$ has the expected appearance but with a slight change of notation to $\alpha_1 = \alpha$, $\alpha_2 = \beta$, $\alpha_3, \ldots, \alpha_n$.

(6) $\quad \widehat{m}_{i_1 \ldots i_n} = \widehat{\mu} + \widehat{(\alpha_1)}_{i_1} + \widehat{(\alpha_2)}_{i_2} + \ldots + \widehat{(\alpha_1 \alpha_2)}_{i_1 i_2} + \ldots + \widehat{(\alpha_1 \alpha_2 \ldots \alpha_n)}_{i_1 i_2 \ldots i_n}$

wherein all possible combinations of subscripts appear (unless known or shown to be zero).

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The method of obtaining the preceding estimates on the right side of the equation turns out to be a recursion formula in terms of estimates having fewer subscripts. Let $\Pi \ell = \ell_1 \ell_2 \ldots \ell_n$. Then

$$(7) \qquad (\widehat{\alpha_1 \alpha_2 \ldots \alpha_r})_{i_1 \ldots i_r} = \frac{\ell_1 \ldots \ell_r}{\Pi \ell} \sum_{i_{r+1} \ldots i_n} y_{i_1 i_2 \ldots i_r i_{r+1} \ldots i_n}$$

$$- (\widehat{\alpha_1})_{i_1} - \ldots - (\widehat{\alpha_r})_{i_r} - (\widehat{\alpha_1 \alpha_2})_{i_1 i_2} - \ldots - (\widehat{\alpha_2 \ldots \alpha_r})_{i_2 \ldots i_r} - \widehat{\mu} .$$

Actually, all possible combinations of the $\alpha_1, \ldots, \alpha_r$ but less than r in number are to be used, and all with minus signs.

By the above methods one can obtain least squares estimates of the parameters supposedly describing an underlying system. Thus if analysis of variance of a factorial experiment indicates that only main effects and no interactions are significant, one generally assumes that any families of curves depicting the underlying facts are sensibly parallel systems. The observed values will of course not give rise to such a parallel appearance, so it seems reasonable to present to the reader a set of curves having the parallel property and also fitting the data closest in the sense of least squares. If the first order interaction is found not to be zero, then likewise the (nonparallel) systems of curves can be found from the estimated parameters, which curves contain the assumed interaction effects and are still best fitting to the observed data in the sense of least squares.

IV. ORTHOGONAL SQUARES DESIGNS

When it is known that there is no interaction among the independent variables, the orthogonal squares designs may be used. These can involve essentially the same large coverage of both numbers of variables and levels of each but requiring only a fraction as many experimental points or values. Of course, the total information, which will include precision of estimates and power of significance tests, is correspondingly reduced. Under the preceding circumstances, formulas similar to (4), (5), (6), and (7), without any interaction terms and with all variables having the same number of levels, ℓ_1, for example, as required by the experimental design, are still valid.

Example

It is one of the orthogonal squares designs, called a Latin square, which we shall apply to a hypothetical experiment to estimate fractionated dose recovery effects. In setting up an actual experiment, much consideration should be given to the pros and cons of using a factorial versus orthogonal squares or other design, since so much depends on the existence or nonexistence of interactions. However, we are now about to introduce an experiment merely as a vehicle to illustrate properties of orthogonal squares designs. The experimental design itself will appear naturally in the course of describing the experiment somewhat in detail.

The Discussion of the Experiment

It is desired to estimate the effect of dose delivered in one period, number of such doses and time between doses, on recovery. Assume a fixed dose rate for all

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exposures. Let the $LD_{50/30}$ be the immediate measure of dose effect, i.e., an increase in the $LD_{50/30}$ indicates a repair mechanism, although other effects could be used, e.g., mitotic index, and the same analyses performed and kinds of conclusions drawn.

Procedure

Determine the $LD_{50/30}$ for a single dose at the dose rate to be used during the exposures, if a good estimate is not already known. Call it Δ.

A group of animals, say 50, will be given a partial or fractionated dose of Δ/k followed by a stated time interval. Then another partial dose of the same size is given. This is repeated a specified number of times. After this same time interval has elapsed, the remaining animals are used to find the residual $LD_{50/30}$.

Some animals may have died before this last phase. We state our interest to be in those that survive to this point. Since animals dying before this stage tend to confound or bias the interpretation of the results, it seems that the total stress or dose to this point should be kept small enough to minimize such effects.

We define and estimate recovery as follows. Let P denote a point in time relative to which the $LD_{50/30}$ is to be obtained in the experimental setup. This is of course after a prescribed number of alternate doses and intervals. Let the sum of fractionated doses to that point equal d and the $LD_{50/30}$ at P for preirradiated animals at P be Δ'. Thus under these conditions a total dose of $d + \Delta'$ is expected to be administered at P to achieve $LD_{50/30}$. But for a single dose the $LD_{50/30} = \Delta$. So $d + \Delta' - \Delta$ = the excess dose required under the conditions of P.

$(d + \Delta' - \Delta)/d$ = the fraction of the total dose, just prior to administering the additional Δ' dose, which is recovered, or from which recovery is made. For example, if $\Delta' = \Delta$, there is complete recovery, and if $d + \Delta' = \Delta$, there is no recovery.

Let the fraction recovered, $(d + \Delta' - \Delta)/d$, be found at each of the experimental conditions, P. This will be the main dependent variable y in the analysis.

Let us now define the variables, recalling that in this design all variables must have the same number of levels.

Let dose A have four levels, e.g.,

$$a_1 = \Delta/5, \ a_2 = 2\Delta/5, \ a_3 = 3\Delta/5, \ a_4 = 4\Delta/5.$$

Let B denote the number of fractionated doses.

$$b_1 = 1, \quad b_2 = 2, \ b_3 = 3, \ b_4 = 4.$$

Let C denote interval in days between fractionated doses.

$$c_1 = 1, \ c_2 = 2, \ c_3 = 3, \ c_4 = 4.$$

Maximum information would be obtained by subjecting a group of animals to each of all possible conditions a_i, b_j, c_k, a total of $4^3 = 64$ groups. Since that many groups are considered to be a prohibitive expenditure of animals and time, it is proposed as mentioned previously, to use an experimental design known in the trade as a Latin square, which will use only 16 of the above conditions. An example of such a design follows.

	a_1	a_2	a_3	a_4
b_1	c_1	c_2	c_3	c_4
b_2	c_2	(c_1)	c_4	c_3
b_3	c_3	c_4	c_1	c_2
b_4	c_4	c_3	c_2	c_1

Figure 2.   Latin Square Experimental Design

The circled position denotes condition a_2, b_2, c_1. y, the fraction of total dose recovered (as defined previously) will be found at all 16 conditions. Then, under the assumption of additivity (i.e., zero interactions), one can estimate the y values corresponding to all the remaining conditions, as explained in the main text later. Note the symmetry in the above configuration in that each c subscript occurs once and therefore only once in every row and column.

Qualitative sketches of traces of the functional form would probably appear as below in Figure 3.
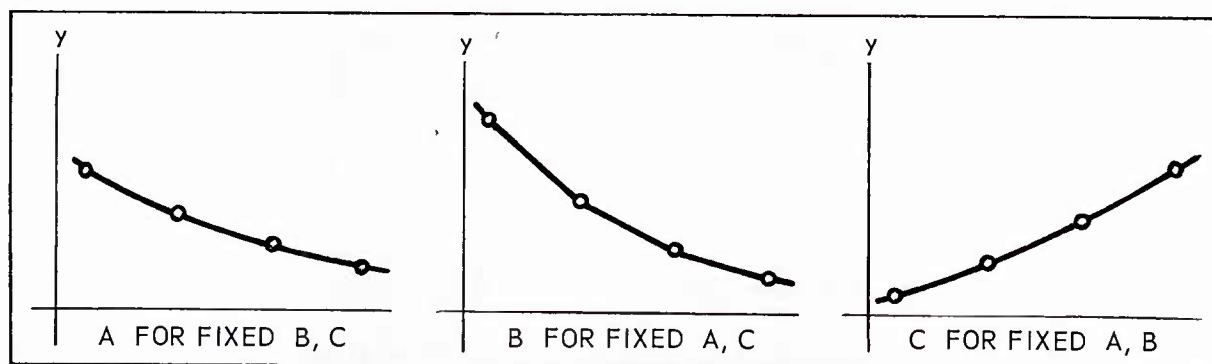

Figure 3.   Qualitative Traces of Function y

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With these 64 values, one is in position to attempt curve and surface fitting $y = f(A, B, C)$ in order to descriptively mathematize the results.

If some measurable and meaningful effect on the individual animal could be used as a measure of the recovery effect instead of the animal devouring, time consuming $LD_{50/30}$ to y, one could afford perhaps to go to the complete factorial design and thus test the significance of the possible interactions. In this case the number of levels of the variables need not be the same. Or one might use larger animals in the experiment.

Now in the same example experiment it would be possible to include a new variable D which is the dose rate. Let d_1 denote 10 rad/min, d_2 denote 100 rad/min. Another orthogonal squares experimental design could then be used as follows.

	a_1	a_2	a_3	a_4
b_1	$c_1 d_1$	$c_2 d_2$	$c_3 d_3$	$c_4 d_4$
b_2	$c_2 d_3$	$c_1 d_4$	$c_4 d_1$	$c_3 d_2$
b_3	$c_3 d_4$	$c_4 d_3$	$c_1 d_2$	$c_2 d_1$
b_4	$c_4 d_2$	$c_3 d_1$	$c_2 d_4$	$c_1 d_3$

Figure 4. Graeco-Latin Square Experimental Design

Now let $d_3 = d_1$, $d_4 = d_2$, for example, since there are only two distinct levels of this D variable.

Consider any letter and subscript, e.g., d_1. It occurs once and only once with every other letter-subscript combination. This design also requires only 16 animal groups as did the previous one. In the same manner the remaining

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$4^4 - 16 = 256 - 16 = 240$ values could be filled in. However, do not be misled into thinking there is more independent information in the 256 points than in the 16 points. It is just that the completed display may suggest some otherwise unperceived information.

We now need the estimation formulas for this case.

Derivation of the Estimation Formulas

The derivation and results are essentially the same as for the factorial case. The differences are in the missing interaction terms like $(\alpha\beta)_{ij}$, and summations like $\underset{j,k}{\sum} y_{ijk}$ which are restricted to the i, j, k combinations displayed in the experimental design. In fact, just as an explicit reminder we write such summations as $\underset{j,k}{\sum'} y_{ijk}$. The prime (') is to remind us that the i, j, k values are restricted to combinations found in the experimental design.

Again we assume that

(8)
$$m_{ijk} = \mu + \alpha_i + \beta_j + \gamma_k ,$$

but with no interaction terms.

i, j, k = 1, ..., ℓ_1 subject to the restriction that in combination they represent one of the conditions of the experimental design. By analogy with the 4-level Latin square displayed previously, this subset of combinations is ℓ_1^2 in number out of the possible ℓ_1^3 total combinations.

(9)
$$y_{ijk} = m_{ijk} + e_{ijk} ,$$

where e_{ijk} is again a normal variate with zero mean and variance σ^2 (usually unknown).

We seek to minimize

$$A = \underset{i,j,k}{\sum'} (y_{ijk} - m_{ijk})^2 = \underset{i,j,k}{\sum'} (y_{ijk} - \mu - \alpha_i - \beta_j - \gamma_k)^2 .$$

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Set $\quad \dfrac{\partial A}{\partial \mu} = -2 \sum'_{i,j,k} (y_{ijk} - \mu - \alpha_i - \beta_j - \gamma_k) = 0 \ .$

Each of α_i, β_j, γ_k are summed over their ℓ_1 values and therefore by assumption each adds up to zero, the same assumption we made in the factorial design. If the $\alpha_1 + \alpha_2 + \ldots + \alpha_{\ell_1} = 0.1$ for example, we would just diminish each α_i by $0.1/\ell_1$ and add 0.1 to the μ. It would not affect their differences, and it is only their differences that really count. So

$$\sum'_{i,j,k} y_{ijk} - \ell_1^2 \mu = 0 \ ,$$

or the least squares estimate of μ is

(10) $\qquad \widehat{\mu} = \dfrac{1}{\ell_1^2} \sum'_{i,j,k} y_{ijk} \ .$

Next

$$\dfrac{\partial A}{\partial \alpha_i} = -2 \sum'_{j,k} (y_{ijk} - \mu - \alpha_i - \beta_j - \gamma_k) = 0 \ ,$$

$$\sum'_{j,k} y_{ijk} - \ell_1 \mu - \ell_1 \alpha_i = 0$$

since again $\sum'_{j,k} \beta_j = 0$ and $\sum'_{j,k} \gamma_k = 0$, each being summed over its respective total set of values. Therefore,

(11) $\qquad \widehat{\alpha_i} = \dfrac{1}{\ell_1} \sum'_{j,k} y_{ijk} - \widehat{\mu}$

where μ must be replaced by its estimate in the solution.

Following exactly similar argument,

(12) $\qquad \widehat{\beta_j} = \dfrac{1}{\ell_1} \sum'_{i,k} y_{ijk} - \widehat{\mu}$

(13) $\qquad \widehat{\gamma_k} = \dfrac{1}{\ell_1} \sum'_{i,j} y_{ijk} - \widehat{\mu} \ .$

The least squares estimate of any particular m_{ijk}, the underlying true mean at the a_i, b_j, c_k combination of levels, whether or not this combination occurs in the experimental design used, would be obtained by substituting component estimates like

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(10), (11), (12) and (13) into (8), giving

(14)
$$\widehat{m}_{ijk} = \widehat{\mu} + \widehat{\alpha_i} + \widehat{\beta_j} + \widehat{\gamma_k} .$$

Numerical Computations

Let us place some hypothetical numerical values for y in the four-level three-variable Latin square table displayed in the section on the recovery experiment. The y values are percent recovery and are displayed in the table below.

Table I. Experimental Values

	a_1	a_2	a_3	a_4
b_1	c_1 72.2	c_2 74.5	c_3 75.9	c_4 68.0
b_2	c_2 74.0	c_1 58.1	c_4 66.1	c_3 50.9
b_3	c_3 77.1	c_4 62.4	c_1 26.9	c_2 26.7
b_4	c_4 56.9	c_3 42.8	c_2 20.5	c_1 1.8

$$\widehat{\mu} = \frac{1}{16}(72.2 + 74.5 + \ldots + 1.8) = \frac{854.8}{16} = 53.425 .$$

Using equations (11), (12), (13) one obtains Table II. As an example

$$\widehat{\gamma_2} = \frac{1}{4}(74.5 + 74.0 + 26.7 + 20.5) - 53.425 = -4.500 .$$

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Table II.   Estimates of α_i, β_j, γ_k

i	$\widehat{\alpha_i}$	$\widehat{\beta_i}$	$\widehat{\gamma_i}$
1	16.625	19.225	− 13.675
2	6.025	8.850	− 4.500
3	− 6.075	− 5.150	8.250
4	− 16.575	− 22.925	9.925

We are now ready to fill out the entire table of

$$\widehat{m}_{ijk} = \widehat{\mu} + \widehat{\alpha_i} + \widehat{\beta_j} + \widehat{\gamma_k}$$

if we so desire.   For example,

$$\widehat{m}_{124} = \widehat{\mu} + \widehat{\alpha_1} + \widehat{\beta_2} + \widehat{\gamma_4} = 53.425 + 16.625 + 8.850 + 9.925 = 88.825.$$

See Table III for the complete set of entries.
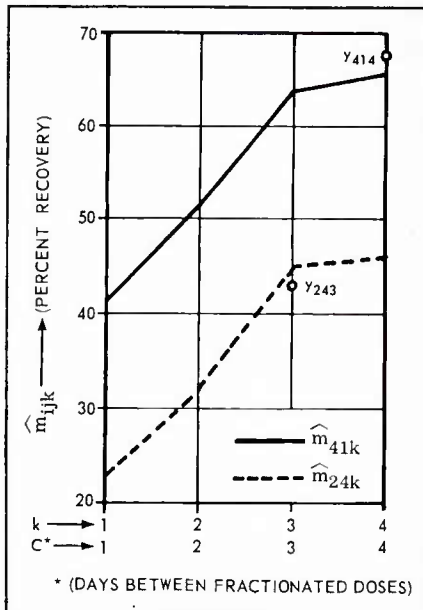
Figure 5.   Graphs of $\widehat{m}_{24k}$, $\widehat{m}_{41k}$ as Function of C.

Next let us graph $\widehat{m}_{ijk}$ (estimate of true y average) as a function of interval between doses (C), for level 2 of dose (A), and for level 4 of (B) which is four doses.   The values to be graphed are $\widehat{m}_{24k}$, k = 1, 2, 3, 4.   They can be read from Table III.   For comparison let us also graph $\widehat{m}_{41k}$ corresponding to one dose applied at the highest level (Figure 5).   These values are shown in Table IV.   It is evident that a large number of such choices could be made, including even plotting a surface $\widehat{m}_{ijk}$ as a function of two of the variables for a fixed value of the third one.

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Table III. Estimates of m_{ijk}

i j k	$\widehat{m}_{ijk}$	i j k	$\widehat{m}_{ijk}$
(1 1 1)	75.600	3 1 1	52.900
1 1 2	84.775	3 1 2	62.075
1 1 3	97.525	(3 1 3)	74.825
1 1 4	99.200	3 1 4	76.500
1 2 1	65.225	3 2 1	42.525
(1 2 2)	74.400	3 2 2	51.700
1 2 3	87.150	3 2 3	64.450
1 2 4	88.825	(3 2 4)	66.125
1 3 1	51.225	(3 3 1)	28.525
1 3 2	60.400	3 3 2	37.700
(1 3 3)	73.150	3 3 3	50.450
1 3 4	74.825	3 3 4	52.125
1 4 1	33.450	3 4 1	10.750
1 4 2	42.625	3 4 2	19.925
1 4 3	55.375	3 4 3	32.675
(1 4 4)	57.050	3 4 4	34.350
2 1 1	65.000	4 1 1	42.400
(2 1 2)	74.175	4 1 2	51.575
2 1 3	86.925	4 1 3	64.325
2 1 4	88.600	(4 1 4)	66.000
(2 2 1)	54.625	4 2 1	32.025
2 2 2	63.800	4 2 2	41.200
2 2 3	76.550	(4 2 3)	53.950
2 2 4	78.225	4 2 4	55.625
2 3 1	40.625	4 3 1	18.025
2 3 2	49.800	(4 3 2)	27.200
2 3 3	62.550	4 3 3	39.950
(2 3 4)	64.225	4 3 4	41.625
2 4 1	22.850	(4 4 1)	0.250
2 4 2	32.025	4 4 2	9.425
(2 4 3)	44.775	4 4 3	22.175
2 4 4	46.450	4 4 4	23.850

The circled combinations appeared in the experiment.

Table IV. Estimates of m_{24k} and m_{41k}

k	$\widehat{m}_{24k}$	$\widehat{m}_{41k}$
1	22.850	42.400
2	32.025	51.575
3	44.775	64.325
4	46.450	66.000

For interest, the experimental values of the only two conditions corresponding to points above are read from Table I and plotted. They are $y(a_2, b_4, c_3) = 42.8$ and $y(a_4, b_1, c_4) = 68.0$. Equivalent notation would let us write these as $y_{243} = 42.8$ and $y_{414} = 68.0$.

* * * * * * *

The subject should not be closed without pointing out another possible and important application. This is in estimating the effects of combined radiation, thermal and blast stresses on the organism. Note that this would be a three-variable system in the simplest experiment. A factorial or fractional replication factorial to estimate interaction terms would surely be required. Again the estimated terms in equations like (6) and (7) are the required effects; (6) gives the combined effects and (7) gives the separate effects of main variables and interactions. It would require an experimental environment wherein different prescribed levels of the three types of insult could be administered, either simultaneously or nearly so.

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A statistical technique is explained, derived and illustrated. It is believed that a study of the values of the terms of the assumed mathematical model (or the graphs therefrom) would be of great informational help to the scientist in interpreting his results. Analysis of variance, components of variance analysis, and the estimation technique described herein applied to a properly designed experiment will go far toward extracting all the relevant information from a sample.

Estimation formulas for the terms of the assumed mathematical model are derived for two of the most used statistical experimental designs, the factorial and the orthogonal squares. The method is illustrated on a three-variable, hypothetical dose recovery experiment.

It is pointed out that the method gives one a handle on measuring quantitatively the separate and joint contributions to the observed effect, of variables otherwise hopelessly correlated and overlapping.

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